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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Signed Stephen Hordley

Dated 12 July 2004

Patents Form 1/77

The Patent Office

1/77

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27JUN03 E818175-1 C22964
P01/7700 0.00-0314944.0

THE PATENT OFFICE
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26 JUN 2003
NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference — IBST 090 — 26 JUN 2003

2. Patent application number *(The Patent Office will fill in this part)* — 0314944.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   CRANFIELD UNIVERSITY
   CRANFIELD
   BEDS, MK43 0AL, UK

   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation — 4100645384300 7. ~~6434740005~~

4. Title of the invention — ELECTROCHEMICAL DETECTOR FOR METABOLITES IN PHYSIOLOGICAL FLUIDS

5. Name of your agent *(if you have one)*

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   ~~CRANFIELD UNIVERSITY~~
   ~~SILSOE~~
   ~~BEDFORDSHIRE, MK45 4DT, UK.~~

   MEWBURN ELLIS LLP
   YORK HOUSE
   23 KINGSWAY
   LONDON
   WC2B 6HP

   Patents ADP number *(if you know it)* — ~~7656473002~~ 109006

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

   FS1/77 28/6 HP

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
—		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
—	

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

   YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	—
Description	2
Claim(s)	—
Abstract	— DL
Drawing(s)	3 only

10. If you are also filing any of the following, state how many against each item.

Priority documents	—
Translations of priority documents	—
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	—
Request for preliminary examination and search *(Patents Form 9/77)*	—
Request for substantive examination *(Patents Form 10/77)*	—
Any other documents *(please specify)*	—

11. I/~~We~~ request the grant of a patent on the basis of this application.

Signature L Sidgwell Date 25-06-03

12. Name and daytime telephone number of person to contact in the United Kingdom

LINDA TIGWELL
01525 863168

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

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ELECTROCHEMICAL DETECTOR FOR METABOLITES IN PHYSIOLOGICAL FLUIDS

Introduction

The concentrations of metabolites in body fluids, particularly in blood, are key indicators to the physiological state of the body. Monitoring of these metabolites is therefore desirable when disease is present or suspected. For example, the level of glucose in blood provides information on the status of a diabetic patient.

There exist many analytical techniques for measuring metabolites in physiological fluids. These fall into three main categories: (i) procedures performed in a specialised laboratory, (ii) techniques executed by a healthcare professional at the bedside or (iii) devices designed for personal use. Glucose testing is a good example which falls into all three areas. Frequent testing of blood glucose is critical to controlling diabetes. The Diabetes Control and Complication Trial (DCCT), a 10-year study carried out by the National Institutes of Health, found that people who test their blood glucose four times or more each day can lower their risk of developing eye, kidney and nerve diseases and high cholesterol. Medical doctors recommend glucose measurements should be made a number of times per day until stabilized.

Background to the Invention

The invention relates to the measurement of metabolites in body fluids using a novel electrochemical sensor system. In one embodiment, the sensor may be used for measuring glucose and other metabolites in interstitial fluid (fluid which exists between cells). When used in combination with a suitable method of extracting interstitial fluid from skin, the sensor offers a highly effective and essentially non-invasive means of monitoring glucose and other metabolites.

Direct electrochemical detection of glucose in blood is notoriously difficult, due the many large molecules that foul the electrode. By performing the analysis in interstitial fluid instead, this problem is mitigated as most of the plasma protein molecules are too large to pass through the capillary walls into the interstitial area. Furthermore, the invention incorporates electrochemical cleaning of the electrode surface to remove fouling agents, and produces multivariate responses which allows the effects of any remaining interferents to be negated using subsequent data processing.

Technical Description

Sensor Construction

The device consists of a noble metal electrode such as platinum or gold in combination with a reference electrode such as silver/silver chloride. A third counter may also be used alongside the other electrodes. The working electrode is surrounded by a highly alkaline microenvironment, to aid electrode cleaning. This environment can be achieved using an alkaline polymer electrolyte or a hydrogel impregnated with basic electrolytes (an example is agarose gel with NaOH). Other materials may also be used for this purpose. Alternatively, volumes of basic electrolytes such as NaOH can be used to dilute the fluid prior to electrochemical analysis.

Electrochemical Measurements

The sensor assembly is placed into the sample matrix of interest, for example interstitial fluid containing glucose. The three electrodes are electrically connected to a potentiostat instrument capable of performing voltammetry.

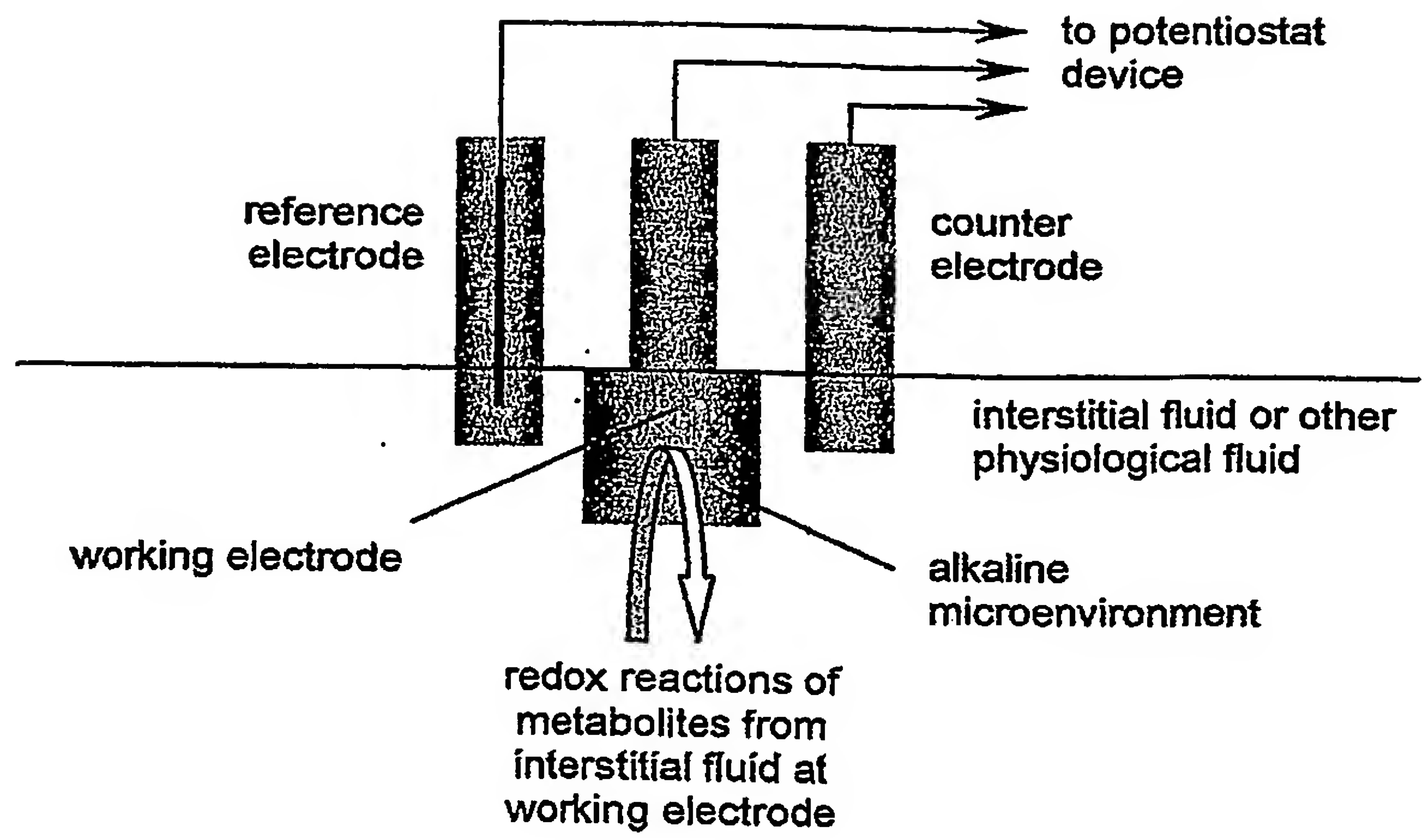

Figure 1: *Diagram showing the experimental set-up of the sensor.*

A potential is applied at the working electrode, following the waveform shown in Figure 2. This consists of two cleaning pulses, which clear the electrode of any electrochemical breakdown products from previous measurements, followed by a voltammetric sweep during which current measurement takes place. The whole measurement, which takes just a few seconds, results in a current *versus* potential response such as that shown in Figure 3.

Simple parameters extracted from the observed data, such as peak height, can be calibrated to give the concentration of individual metabolites of interest. However, further chemometric processing using, for example, the multivariate regression abilities of feed forward neural networks (Figure 4) can be used to provide more accurate measurements. Such chemometric methods also allow the quantification of more than one analyte from a single measurement, as each analyte is typically active a particular point in the voltammetric sweep.

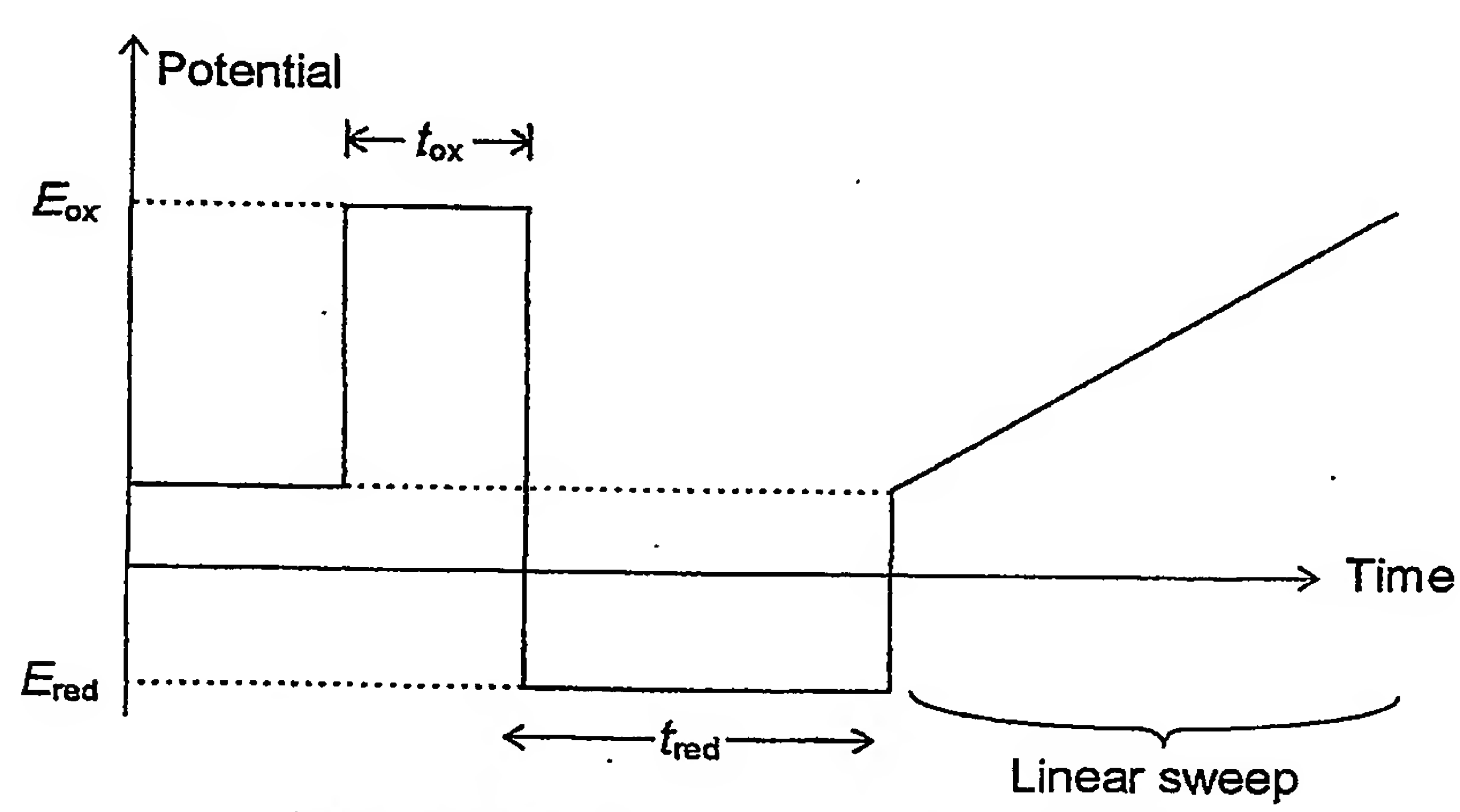

Figure 2: *Applied potential waveform.*

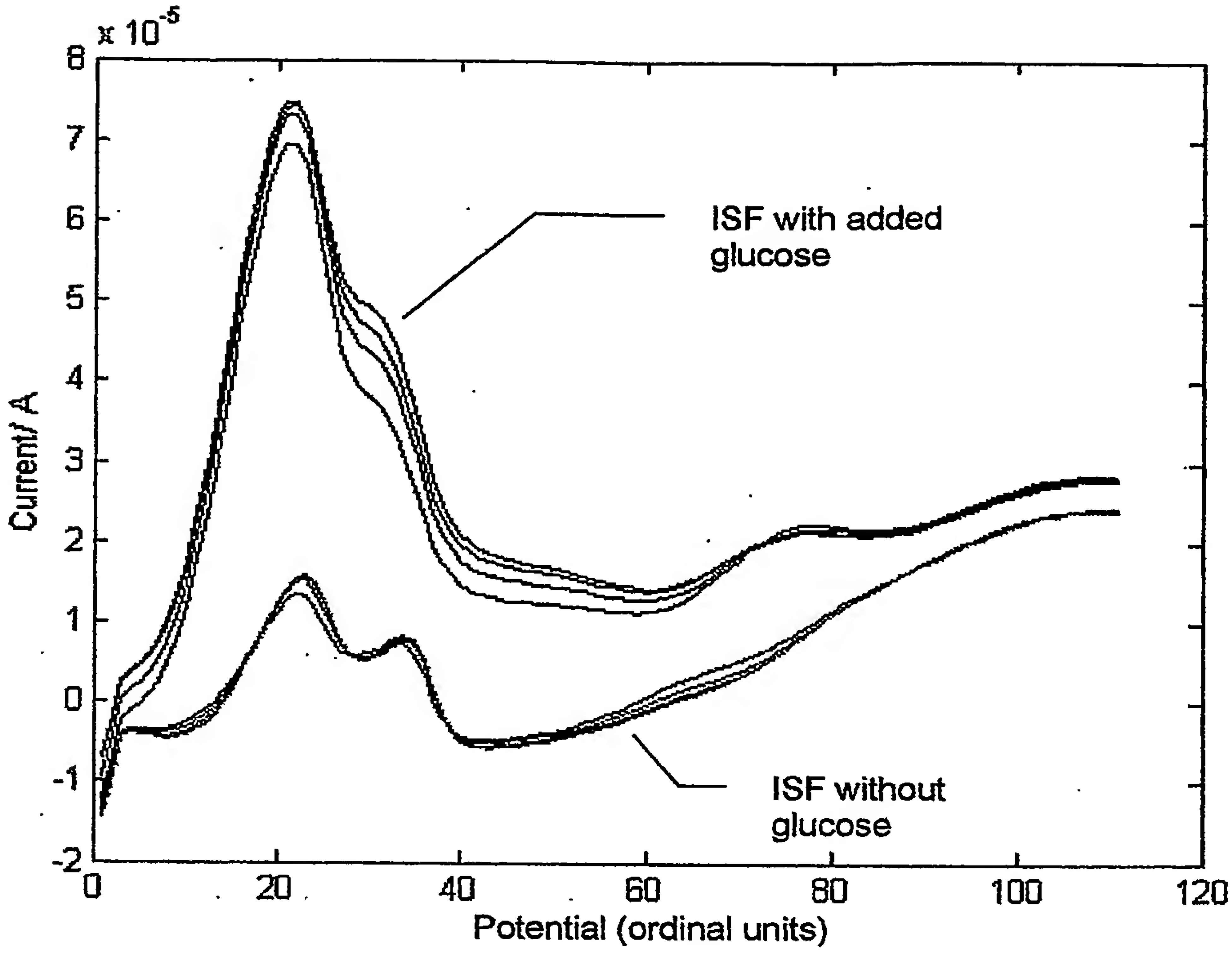

Figure 3: *Example of current response acquired from the sensor, in this case for interstitial fluid spiked with glucose. The potential range scanned in this case was approximately -0.9V to 0.2V.*

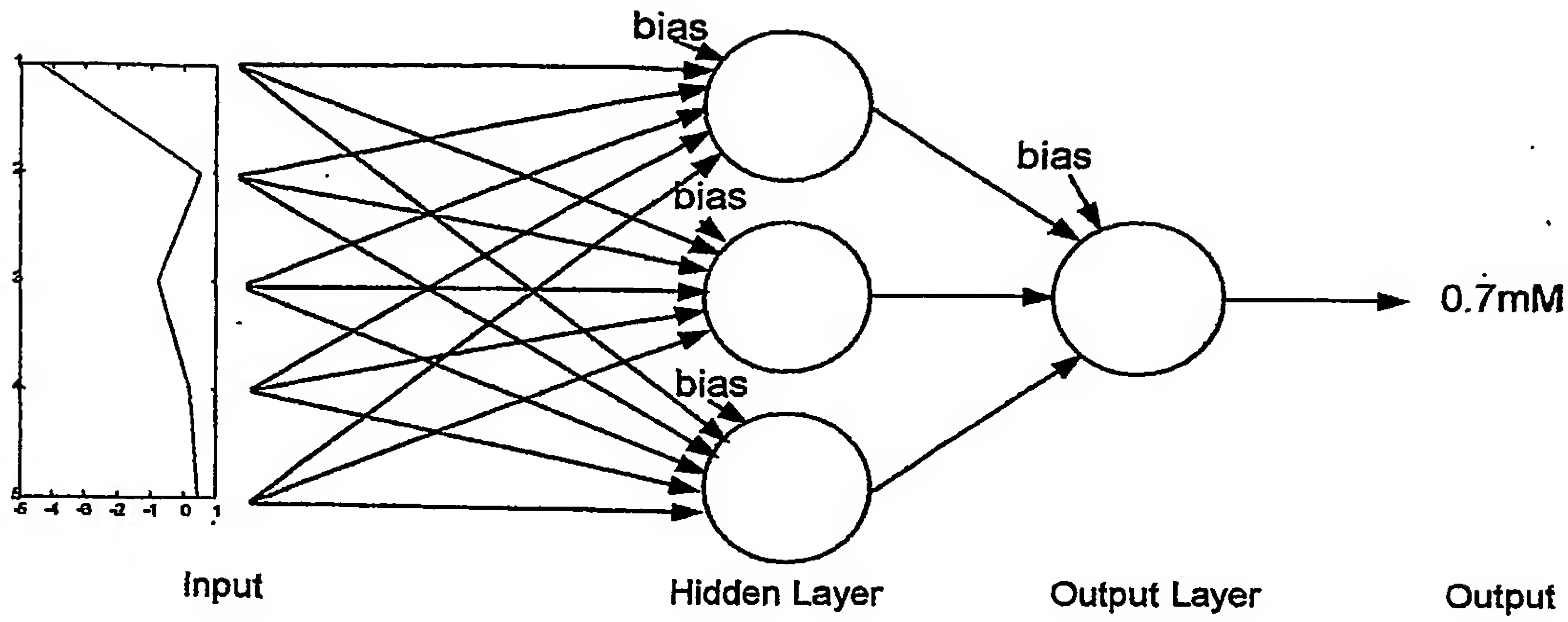

Figure 4: *Neural network calibration of sensor data. In this case, the number of inputs to the network is optimsed by reducing the number of points in the acquired voltammogram using linear algebra.*

Benefits of Invention

The sensor device is capable of simultaneously measuring several analytes in body fluids in a single measurement cycle. Particularly useful features of the invention are:

1. High sensitivity for certain metabolites such as glucose, permitting application in small volumes, such as those associated with interstitial fluids.

2. The ability to self-clean between each measurement.

3. High stability of the sensor.

4. Opportunity to measure more than one metabolite simultaneously.

5. Speed of measurement (<5 seconds).

6. Potential small size of low cost of equipment, allowing embodiment of the invention as a patient operated device or autonomous system.